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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Thomas Bork HARDAHL et al.	:	Date of NOA: 04/15/2011
Application No. 10/596,617	:	Group Art Unit 3762
Filed: 02/05/2007	:	Examiner: Joseph M. Dietrich
For: SYSTEM AND A METHOD FOR ANALYSING ECG CURVATURE FOR LONG QT SYNDROME AND DRUG INFLUENCE	:	Confirmation No. 8471

RESPONSE TO NOTICE TO FILE CORRECTED APPLICATION PAPERS NOTICE OF ALLOWANCE MAILED

Mail Stop Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Enclosed please find pages 7, 10, 13, 16, 23, 24 & 26 of the specification for the above-identified application for review by the U.S. Patent and Trademark Office in connection with the Notice to File Corrected Application Papers Notice of Allowance Mailed dated June 21, 2011. Should the enclosed pages of the specification be unacceptable, it is respectfully requested that the U.S. Patent and Trademark Office notify the undersigned attorney of same.

Respectfully submitted,

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$$m_0 = \sum_{n=Tstart}^{Tend} v[n]$$

and v[n] is the ECG signal.

S9 Variation with Tpeak as mean evaluated in a symmetric interval of 10% of the Tstart-Tend-interval surrounding Tpeak, calculated by the formula:

$$S9 = \left(\sum_{n=Tpeak-0.05\cdot(Tend-Tstart)}^{Tpeak+0.05\cdot(Tend-Tstart)} (n-Tpeak)^2 \cdot w[n] \right)^{\frac{1}{2}},$$

where $w[n] = v[n]/m_0$,

$$m_0 = \sum_{n=Tstart}^{Tend} v[n]$$

and v[n] is the ECG signal.

S10 Variation with Tpeak as mean evaluated in a symmetric interval of 20% of the Tstart-Tend-interval surrounding Tpeak, calculated by the formula:

$$S10 = \left(\sum_{n=Tpeak-0.1\cdot(Tend-Tstart)}^{Tpeak+0.1\cdot(Tend-Tstart)} (n-Tpeak)^2 \cdot w[n] \right)^{\frac{1}{2}},$$

where $w[n] = v[n]/m_0$,

$$m_0 = \sum_{n=Tstart}^{Tend} v[n]$$

and v[n] is the ECG signal.

S11 The Hill parameter, K_m, evaluated by least square fitting of the repolarisation integral, RI(t), from the Jpoint to the following Ponset as described by Kanters et al., "T wave morphology analysis distinguishes between *KvLQT1* and *HERG* mutations in long QT syndrome", Heart Rhythm (2004) 3, 285–292:

$$RI(t) = V_{\max}\left(\frac{t^n}{K_m{}^n + t^n}\right)$$

S12 The Hill parameter, K_m, evaluated by least square fitting of the repolarisation integral, RI(t), from Tstart to Tend analogous to the method described by Kanters et al., "T wave morphology analysis distinguishes between *KvLQT1* and *HERG* mutations in long QT syndrome", Heart Rhythm (2004) 3, 285–292:

$$RI(t) = V_{\max}\left(\frac{t^n}{K_m{}^n + t^n}\right)$$

F1 Flatness evaluated from Tstart to Tend, calculated by the formula:

$$F1 = \left(\sum_{n=Tstart}^{Tend} (n-m_1)^4 \cdot w[n] \right)^{\frac{1}{4}},$$

$$F11 = \frac{\sum_{n=Tpeak}^{Tend} v[n]}{Tend - Tpeak},$$

where v[n] is the ECG signal.

F12 Flatness parameter, F11, normalized by the size of the R wave, calculated by the formula:

$$F12 = \frac{F11}{|\, v[Rpeak] - v[Jpo\,\mathrm{int}]|},$$

where v[n] is the ECG signal.

F13 Ratio of the total area under the T-wave from Tstart to Tend and the corresponding time interval, calculated by the formula:

$$F13 = \frac{\sum_{n=Tstart}^{Tend} v[n]}{Tend - Tstart},$$

where v[n] is the ECG signal.

F14 Flatness parameter, F13, normalized by the size of the R wave, calculated by the formula:

$$F14 = \frac{F13}{|\, v[Rpeak] - v[Jpo\,\mathrm{int}]|},$$

where v[n] is the ECG signal.

F15 Ratio of the T wave height and the T wave width, calculated by the formula:

$$F15 = \frac{v[Tpeak]}{Tend - Tstart},$$

where v[n] is the ECG signal.

F16 The T wave height, calculated by the formula:

$F16 = v[\mathrm{Tpeak}]$,
where v[n] is the ECG signal.

F17 Average slope from Tstart to Tpeak, calculated by the formula:

$$F17 = \frac{v[Tpeak] - v[Tstart]}{Tpeak - Tstart},$$

A selection of these parameters is possible so that special genetic combinations are known with reference to the different stored parameters. The system can be updated by new data selected from different sources.

The system and/or method can analyse the QT curvature of the ECG for indicating Long QT syndrome. This way, the Long QT syndrome can be indicated in an objective and effective manner which might occur in postsyncopal cardiac examination.

The method can differentiate between different genotypes of the Long QT Syndrome, which is important for the treatment. It can, hereby, be achieved that the correct medical treatments can be started. The system and the method can be used for test of drug influence on ECG curvature.

The system can be trained, where the parameters' values are calculated for individual subjects, where an analysis of the parameters is performed such as a pattern classification method based on supervised learning, such as Discriminant Analysis, Nearest Neighbor Techniques, Multilayer Neural Networks, Decision Trees and Rule Based Methods or combinations of these.

The final classification function is at least based on data from at least one LQT or drug influenced group and Normal subjects stored as a training set with the consequences that the classification method is improved by adding new subjects to the training set, which new subject can be tailored to demographic or gender differences. In addition it is achieved that reference values based on the training set can be selected from the most critical group of persons with reference to the parameters that are going to be tested.

Once the parameters' values are calculated for individual subjects the mathematical analysis chooses the optimal (small) parameter set out of the complete set (large) from all categories, which values are stored as ref. values. It should be made clear that the final classification functions are based on data from at least one LQT or drug influenced group and Normal subjects (the training set) with the consequences that the discrimination method can be improved, in principle, by adding new subjects to the train-

repolarisation patterns. The most prevalent genes affected in LQTS patients are KvLQT1 and HERG which account for more than 90% of LQTS genotype patients. The current study focuses on carriers of these two genes. Although some attempts have been made to develop quantitative measures that link different repolarisation abnormalities to specific LQTS related channel-opathities these methods have so far failed to provide a solid diagnostic yield. In current practice the duration of the QT interval is the only widely accepted quantifier of ventricular repolarisation. Yet, it has been recognized that the duration of the QT interval is only a gross estimate of repolarisation since T-wave morphology is also important when characterizing the QT interval. This is evidenced by the fact that approximately 10% of all mutation carriers have a normal Bazett corrected QTc (<440ms) and 40% of KvLQT1 and HERG carriers show QTc values between 410-470 ms that overlap with non-carriers. Conversely only 2% of all carriers present with a normal ST-T pattern and a normal QT interval. Morphological aberrations thus carry major implications for the identification of abnormal repolarisation and have been included as diagnostic criteria equivalent to that of a positive family history for LQTS.

Studies have shown that affected KvLQT1 patients generally show broad based T-waves with a normal to relatively high amplitude and often without a distinct T - wave onset. For individuals with mutations involving the HERG gene the aforementioned studies have generally found low amplitude T-waves with bifid T-waves in 60% or more of the carriers.

Cardiologists already include a qualitative assessment of T-wave morphology from the ECG in order to obtain information that augments the clinically established QT interval measurement and facilitates discrimination between LQTS genotypes. However qualitative description of repolarisation morphology may be biased due to intra- and interpersonal variability thus indicating the need for a standardized quantitative measure of this parameter.

In the following is presented a novel multivariate categorization method that allows discrimination between KvLQT1, HERG and normal individuals based on Twave morphology recorded from 12-lead ECG's. Hallmark morphological features of T-

3. Results

The discriminant functions were based on data from all KvLQT1, HERG and normal subjects. The 5 parameters included in both discriminant functions are listed in table 2.

The discriminative efficiency of both generated functions was statistically significant after inclusion of all 5 parameters (function 1: $p<0.0001$, function 2: $p<0.005$).

Variables Entered

Step	Entered
1	F11std
2	QTcmeanV5
3	S5meanV5
4	D4std
5	S4meanV5

Table 2. Variables used by the two discriminating functions. Stepwise introduction of more variables improved the ability of the functions to discriminate between KvLQT1, HERG and normal.

A scatterplot was generated from the discrimination functions and groupings of individual genotypes can be seen in figure 4. The dotted lines were read from the SPSS generated territorial map and manually added. The lines reflect borderlines where the differences between each pair of discrimination functions are zero. All 16 processed ECG's were correctly classified and showed at least one discriminatory characteristic as defined by the 5 parameters included in the discrimination functions. Cross validation of both discriminant functions was done with the leave-one-out method and all 16 subjects were again correctly grouped. Reducing the number of variables resulted in misclassified cases due to lack of one or more discriminatory characteristics. In light of this finding we elected to perform further analysis of the selected parameters in

order to investigate the individual contributions of each variable to the separation of the three primary groups of subjects. Extreme values for all parameters were identified and the mean was computed.

The result is plotted in figure 5. As expected the extent of interlead flatness variation observed in HERG and normal individuals was lower than that found in KvLQT1 subjects. This is evidenced by the F11std parameter in figure 5a. When evaluating parameter values S4meanV5 and S5meanV5 (figure 5b, d) the extent of asymmetry in KvLQT1 and normal was generally less than that of HERG individuals. Both S4meanV5 and S5meanV5 are symmetry parameters and asymmetry in HERG individuals was augmented in two ways: When bifid T-waves were present the interval from Tstart to Ttop was prolonged due to the definition of Ttop used in this study (the last highest point on the T-wave). Also, when the initial portion before Ttop was prolonged in HERG individuals better discrimination was possible. Both phenomena were observed in HERG subjects. Generally the Bazett corrected QTc observed in HERG and KvLQT1 was higher than that of normal individuals (figure 5e). However overlap existed between all three groups preventing separation of the groups by QTc. Since no single parameter included in the discrimination functions was able to separate KvLQT1, HERG and normal, we proceeded to investigate the classification efficiency provided by the three primary categories represented by the parameters in the functions. This was carried out by generating new discrimination functions using parameters from one category only while excluding the other two. Then, from the new discrimination functions three additional functions were generated, this time allowing the inclusion of parameters from combinations of two categories. Scatterplots illustrating the results of this analysis are shown in figures 6a-f. The first two functions (figure 6a) included parameters that characterize the symmetrical properties of the Twave. 83.1% of the 16 subjects were correctly classified. Arrows in figure 6a indicate the 3 misclassified subjects. A second discriminant analysis was performed using flatness parameters. This resulted in 93.8% correctly classified subjects. Only one subject was not correctly classified as indicated by the arrow on figure 6b. The misclassified case was the same HERG subject incorrectly classified using symmetry parameters. The discriminatory efficiency of duration parameters was also evaluated. Discrimination analysis resulted in 93.8% correctly classified subjects. One HERG subject was mis-

Using only symmetry parameters, 3 subjects were misclassified. However no obvious visual characteristics on the three misclassified ECG's could be identified that explained the incorrect classifications. The Bazett corrected QTc was 347ms for the normal subject, 425ms KvLQT1, 476ms HERG. Although an obviously prolonged QTc was present in the misclassified HERG subject it was not identified using symmetry parameters alone.

Discriminant analysis using parameters from the flatness category resulted in only 1 misclassification. Again no visual characteristics were identified to account for the misclassification. Although it was anticipated that the

Figure 6. a) The result of discriminant analysis using symmetry parameters resulted in three misclassified cases (arrows). Visual inspection of the ECG's revealed no apparent abnormalities to indicate the reason for incorrect misclassification. **b)** The result of discriminant analysis using flatness parameters. One incorrectly classified HERG subject was identified (arrow) even though no obvious visual abnormality indicated a different genotype. **c)** Result of discriminant analysis using duration parameters. This result illustrates the failure of duration parameters to discriminate between KvLQT1, HERG and normal (arrow). **d-e**) Combinations of parameters from two categories illustrate the improvement in classification efficiency when compared to figures 6a-c evaluation of T-wave flatness would be able to discriminate HERG from KvLQT1 subjects this was not accomplished by using flatness as a single descriptor of repolarisation. Performing discriminant analysis based on the QTc parameter as the only variable resulted in 1 misclassification. This was not unexpected since it is well known that a substantial overlap in QTc values can exist between normal and affected individuals. The lack of unambiguous discrimination between all groups by use of the QTc parameter alone emphasizes the hypothesis that additional parameters are needed to classify LQTS individuals. By combining parameters from two categories it was found that the discriminatory strength was increased.

(figures 6d-f) This was evidenced by the fact that no subjects were misclassified using two categories. A particularly interesting finding, was the perfect separation of all subjects that was obtained using symmetry and flatness parameters with no duration parameters included. This result implies the discriminatory strength inherent in parame-